FORM PTO-1390 (REV 10-96) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: Beiersdorf 435-MWR

10 JUN 1997

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 08/849525

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP95/04908	12.December.1995	13.December.1994

TITLE OF INVENTION: USE OF FLAVONOIDS AS IMMUNOMODULATING OR IMMUNO-PROTECTIVE AGENTS IN COSMETIC AND DERMATOLOGICAL PREPARATIONS

APPLICANT(S) FOR DO/EO/US: Ghita Lanzendörfer, Franz Stäb and Sven Untiedt

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2)) (TITLE PAGE)
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

(January 1997)

U.S APPLICATION NO (if known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
	PCT/EP95/04908	Beiersdorf 435-MWR

17. [x] The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
Search Report has been prepared by the EPO or JPO $910.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $700.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $770.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1040.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 910.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [x] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	- 20 =		7	X $22.00	$
Independent claims	- 3 =		2	X $80.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $260.00	$
TOTAL OF ABOVE CALCULATIONS =					$1040.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).					$
SUBTOTAL =					$1040.00
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					$
TOTAL NATIONAL FEE =					$1040.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$
TOTAL FEES ENCLOSED =					$1040.00
				Amount to be: refunded	$
				charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [x] Please charge my Deposit Account No. 19-3869 in the amount of $ 1,040.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-3869. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO
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Date of Deposit 6-10-97

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

By: William Mosey

SIGNATURE: M W Russell

Mark W. Russell
NAME

37,514
REGISTRATION NUMBER

Beiersdorf 435-MWR:jg
1120-Dr.Lt/Le

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Ghita Lanzendörfer, Franz Stäb and Sven Untiedt
Serial No.	:	TO BE ASSIGNED
Filed	:	HEREWITH
For	:	USE OF FLAVONOIDS AS IMMUNOMODULATING OR IMMUNO-PROTECTIVE AGENTS IN COSMETIC AND DERMATOLOGICAL PREPARATIONS
Group Art Unit	:	
Examiner	:	

June 10, 1997

Hon. Assistant Commissioner
for Patents
Washington, D.C. 20231

BOX PCT

PRELIMINARY AMENDMENT

Prior to examining the above-identified application on the merits, kindly amend the claims as follows:

IN THE CLAIMS

Cancel all the claims and substitute:

-- 8. A method for the treatment of immunosuppresion of the skin cells induced by UVB radiation and for protecting the cells which participate in the immune response of the skin, said method comprising applying an effective amount of a cosmetic or

dermatological formulation comprising:

a) one or more flavonoids;

b) one or more cinnamic acid derivatives; and

c) optionally an antioxidant

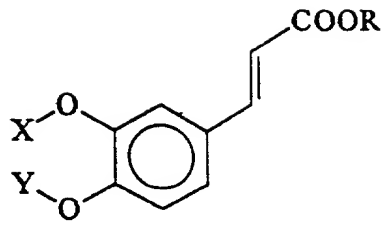
to said skin.

9. The method according to claim 8, wherein the flavonoid is selected from the group consisting of alpha-glucosylrutin, alpha-glucosylmyrictrin, alpha-glucosylisoquercitrinin and alpha-glucosylquercitrin, quercitin, rutin, chrysin, kaempferol, myricetin, rhamnetin, apigenin, luteolin, naringin, hesperidin, naringenin, hesperitin, morin, phloridzin, diosmin, fisetin, vitexin, neohesperidin dihydrochalocone, flavone, glucosylrutin and genistein.

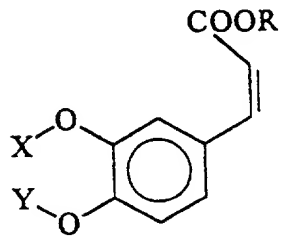
10. The method according to claim 8, wherein the formulation comprises one or more flavonoids and one or more cinnamic acid derivatives.

11. The method according to claim 8, wherein the formulation comprises one or more cinnamic acid derivatives wherein the cinnamic acid derivative is a hydroxycinnamic acid.

12. The method according to claim 8, wherein the formulation comprises one or more cinnamic acid derivatives wherein the cinnamic acid derivative is of the formula



and/or of the formula



wherein the groups X, Y and R independently of one another are H or branched or unbranched alkyl having 1-18 C atoms.

13. The method according to claim 8, wherein the symptom of the immunosuppression is inflammation, allergy or an autoimmune-reactive symptom.

14. A cosmetic or dermatological formulation which comprises an effective amount of:

a) one or more flavonoids;

b) optionally one or more cinnamic acid derivatives;

c) optionally an oxidant; and

d) alpha-glucosylatine and/or ferulic acid. --

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess to our Deposit Account No. 19-3869.

REMARKS

By this amendment, Applicants have placed the claims in compliance with conventional U.S. practice. As these new claims find support in the claims which they replace, no new matter has been added by this amendment.

Favorable action is earnestly solicited.

Respectfully submitted,

SPRUNG KRAMER SCHAEFER & BRISCOE

By: _____

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Description

Use of flavonoids as immunomodulating or immunoprotective agents in cosmetic and dermatological formulations

The present invention relates to active compounds and formulations comprising such active compounds for cosmetic or dermatological treatment and/or prophylaxis of inflammatory, allergic or autoimmune-reactive symptoms, and protecting cells which participate in the immune response of the skin.

As a barrier organ in the human organism, the skin, especially the epidermis, is particularly subjected to external effects. According to current scientific understanding, the skin represents an immunological organ which, as an immunocompetent peripheral compartment, plays its own role in inductive, effective and regulatory immune processes of the total organism.

Light occupies an important position among the physical environmental influences. The damaging effect of the ultraviolet component of solar radiation on the skin is generally known. While rays having a wavelength below 290 nm (the so-called UVC range) are absorbed by the ozone layer in the earth's atmosphere, rays in the range between 290 and 320 nm, the so-called UVB range, cause erythema, simple sunburn or even burns of greater or lesser severity. The narrower range around 308 nm is stated as a maximum for the erythema activity of sunlight.

Ultraviolet light from the wavelength range between about 320 and 400 nm (UVA range) can also cause secondary damage to the skin. It has thus been proved that UVA radiation also leads to damage to the elastic and collagenic fibres of connective tissue, which causes the skin to age prematurely (so-called photoageing), and that it is to be regarded as a cause of numerous photo-

toxic and photoallergic reactions. The damaging influence of UVB radiation may be intensified by UVA radiation.

UVB radiation is of particular interest in the development of topical sunscreen compositions, since the action spectrum for the acutely inflammatory processes (sunburn) and chronic damage (photoageing) is located here.

In addition to these effects, a serious change in the intraepidermal immunological situation may furthermore occur under the action of UVB, this being called UVB-induced immunosuppression. Under certain circumstances, depending on the dose of radiation, far-reaching changes in the immunological processes of the skin with both local and systemic effects are possible consequences here.

Immunosuppression generally is the suppression or attenuation of the reactivity of the immune system. UVB-induced immunosuppression can be classified into local and systemic effects. In the end, it includes a large number of the most diverse aspects, all of which comprise reduction of the normal immunological defence mechanisms of the skin. The increased tumour growth was thus already related to the immunosuppressive action of UVB light very early on using the model of mice irradiated with UVB. This UVB-induced immunosuppresion is nowadays discussed as the mechanism by means of which UVB-induced neoplastic cells, which are in themselves highly immunogenic, withdraw from immunological defence and therefore their own destruction.

There is furthermore a marked decrease in contact hypersensitivity reaction in the case of UVB irradiation compared with some agents which sensitize the skin. The reason for this could lie in a drastic reduction in the number of epidermal Langerhans cells and/or a change in their morphology and functionality. However, Langerhans cells are the afferent arm of the immunological defence of the skin. Effective defence reactions against infectious organisms, such as, for example, Candida albicans or herpes simplex virus, are furthermore absent.

Finally, the expression of "intercellular adhesion molecule-1" on epidermal keratinocytes is suppressed as a consequence of a dermatologically relevant UVB exposure. This glycoprotein on the cell surface (also called ICAM-1) is one of the most important cellular communication structures, via which direct cell-cell contacts between epidermal keratinocytes and leukocytes, such as, for example, T-lymphocytes and monocytes, are regulated.

UVB-induced immunosuppression thus concerns a broad spectrum of immunological dysfunctions which result in a reduction in the defence reactions which normally proceed.

It is indeed customary to use absorbing agents, that is to say the customary light protection substances, against the direct action of ultraviolet radiation.

Derivatives of dibenzoylmethane, for example, are chiefly used for protection against rays in the UVA range.

Many compounds are known for protection against UVB radiation, these chiefly being derivatives of 3-benzylidenecamphor, of 4-aminobenzoic acid, of cinnammic acid, of salicylic acid, of benzophenone and also of 2-phenylbenzimidazole.

It was furthermore also known to employ free radical collectors as agents which act against photo-oxidative symptoms in the skin induced by UV radiation. As is known, such photochemical reaction products are chiefly free-radical compounds, for example hydroxyl radicals or superoxide radical anions. Undefined free-radical photo products which are formed in the skin itself can also show uncontrolled secondary reactions because of their high reactivity. However, singlet oxygen, a non-radical excited state of the oxygen molecule, may also occur under UV irradiation, as may short-lived epoxides and many other reactive oxygen species. Singlet oxygen, for example, is distinguished from the triplet oxygen normally present (free-radical ground state) by an increased reactivity. Nevertheless, excited,

reactive (free-radical) triplet states of the oxygen molecule also exist.

It has thus already been proposed to employ vitamin E or vitamin E esters, substances of known antioxidative action, in light protection formulations. However, the background was always UV protection by absorption of light or protection against photo-oxidative processes. Furthermore, the activity of vitamin E from topical vehicles was weak. A high dosage also provided no remedy, since a more prooxidative action was achieved, especially with vitamin E.

Combinations of 2,4-O-furfurylidenesorbitol, thiols and vitamin E, which are mentioned in PCT/DE93/00773, for intensifying the endogenous immune system of the skin have also fallen short of expectations.

The object of the present invention was therefore, and this object is achieved according to the invention, to provide active compounds and formulations comprising such active compounds, with the aid of which

- a more effective prophylaxis against UVB immunosuppression can be achieved and
- the immune system already damaged by UVB immunosuppression can be strengthened again.

The active compounds and formulations according to the invention act in this way.

It was surprising and not to be foreseen by the expert that the cosmetic or dermatological formulations for treatment and/or prophylaxis of the immunosuppression induced by UVB radiation, characterized by a therapeutically or cosmetically active content of the substance specified below,
and the use of cosmetically or dermatologically acceptable substances specified below for cosmetic or dermatological treatment and/or prophylaxis of the immunosuppression induced by UVB radiation
would achieve these objects.

The substances according to the invention chosen from the group consisting of flavonoids and their

glucosides, from the group of cinnamic acid derivatives and from the group of tocopherols and their derivatives are particularly advantageous.

Japanese Laid-Open Specification Hei-06-138,941 indeed describes oral formulations having a content of water-soluble glucosides, which can be chosen, for example, from the group consisting of α-glucosylrutin, α-glucosylmyrictrin, α-glucosylisoquercitrin and α-glucosylquercitrin. Japanese Laid-Open Specification Hei-04-363,395 describes a process for preventing decomposition of perfume constituents which is distinguished, inter alia, by an addition of α-glucosylrutin to the corresponding formulations. European Laid-Open Specification 586 303 and European Laid-Open Specification 595 694 furthermore describe the use of flavonoids as antioxidants or light protection substances in cosmetics. It is furthermore known from US-A 4,144,325 and 4,248,861 and from numerous other documents to employ vitamin E in cosmetic and dermatological light protection formulations. However, the use according to the invention of vitamin E and its derivatives for cosmetic or dermatological prophylaxis of the immunosuppression induced by UVB radiation was not made obvious by the prior art.

However, no indication which could lead in the direction of the present invention is to be found in these specifications.

The above objects are achieved according to the invention.

The invention relates to the use of cosmetic and dermatological formulations having

a) a content of a compound or several compounds from the group consisting of flavonoids or having

b) a content of an active compound combination comprising a compound or several compounds chosen from the group consisting of flavonoids in combination with a compound or several compounds chosen from the group consisting of cinnamic acid derivatives and

c) if appropriate an additional content of a compound or

several compounds from the group consisting of antioxidants for treatment or prophylactic treatment of the immunosuppression induced by UVB radiation, in particular for treatment or prophylactic treatment of inflammatory, allergic or autoimmune-reactive symptoms, and for protecting cells which participate in the immune response of the skin.

Active compound combinations b), their use and formulations which comprise these are preferred.

The invention also relates to the use of the active compound according to the invention for the purposes mentioned and their use as immunomodulating or immunoprotective active compounds, in particular in cosmetic and dermatological formulations.

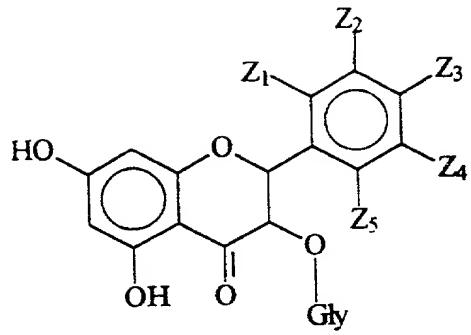
The active compounds and formulations according to the invention are used for protection of immunocompetent cells, such as Langerhans cells, and for protection of cell constituents.

Topical formulations are preferred.

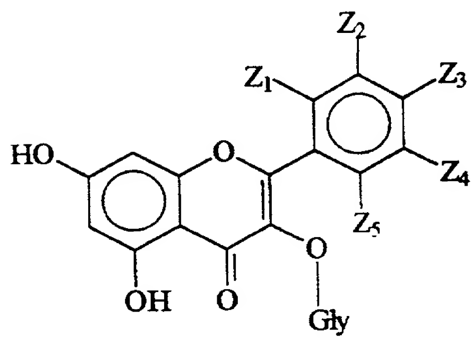
Preferred flavonoids according to the invention are, for example, hydroxylated flavones, flavanones, isoflavones or chalcones, and in each case also glycosides thereof, as well as these non-hydroxylated base structures and parent substances.

The flavonoids according to the invention are also designated A) below, the cinnamic acid derivatives according to the invention are designated B) and the antioxidants according to the invention are also designated C).

According to the invention, the flavonoids A) are preferably chosen from the group consisting of substances of the generic structural formulae



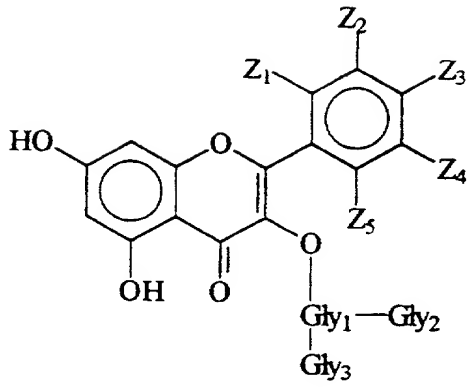
and



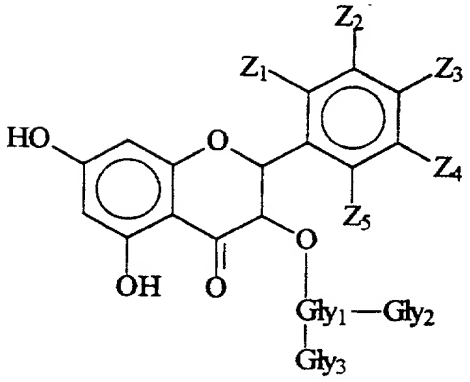
,

wherein Z_1-Z_5 independently of one another are chosen from the group consisting of H, OH and O-alkyl, wherein the alkyl groups can be branched and unbranched and can contain 1-10 C atoms, and wherein Gly is chosen from the group consisting of mono- and oligoglycoside radicals, or can also be H. Preferred glycoside radicals are those mentioned below for Gly_1-Gly_3.

Further flavonoids according to the invention are advantageously chosen from the group consisting of substances of the following formulae:



and



wherein Z_1-Z_5 have the abovementioned meanings and Gly_1, Gly_2 and Gly_3 are monoglycoside radicals.

Preferably, Gly_1, Gly_2 and Gly_3 independently of one another are chosen from the group consisting of hexosyl radicals, in particular the rhamnosyl radicals and glucosyl radicals. However, other hexosyl radicals, for example allosyl, altrosyl, apiosyl, arabinosyl, biosidyl, galactosyl, gulosyl, glucoronidyl, idosyl, mannosyl, talosyl and xylosyl, are also advantageously to be used, where appropriate. It may also be advantageous according to the invention to use pentosyl radicals.

It is particularly advantageous in the context of the present invention to choose the flavone glycoside or glycosides from the group consisting of alpha-glucosyl-rutin, alpha-glucosylmyrictrin, alpha-glucosylisoquercitrin and alpha-glucosylquercitrin.

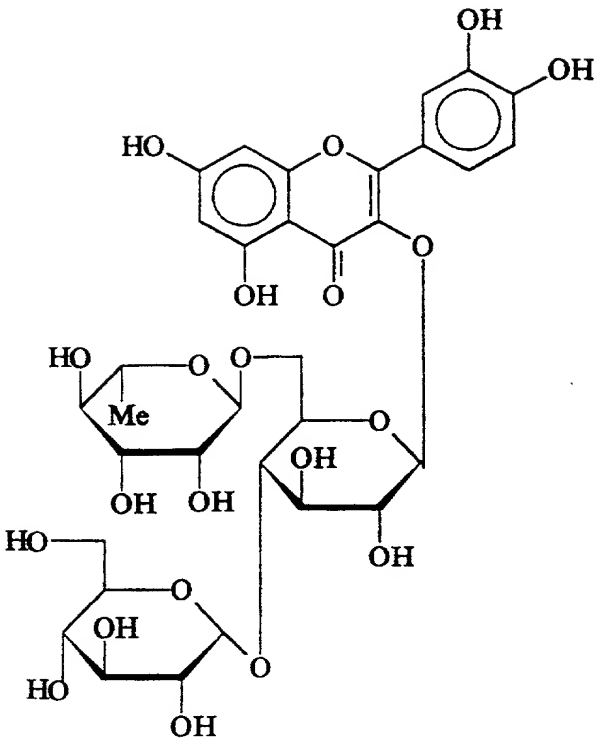
Compounds such as alpha-glycosylrutin, alpha-glycosylhesperidin, alpha-glycosylnaringin, alpha-mannosylrutin and alpha-rhamnosylrutin are furthermore particularly preferred according to the invention.

It may also be advantageous to omit the above-mentioned glycosidic radicals Gly_{1-3} and to use the unsubstituted flavonoids (Gly_{1-3} = H), such as, for example, quercitin. It may also be of advantage to use flavonoids in which the glucoside radical is bonded to C7, C4', C3' or C5' via phenolic OH functions.

It may furthermore be advantageous to use flavonoids in which the phenolic OH function on C9 is present in the free form (so-called chalcones). It is particularly advantageous to use neohesperidin dihydrochalcone from this group.

It is advantageous in the context of the present invention to choose the flavonoid or flavonoids from the group consisting of quercitin, rutin, chrysin, kaempferol, myricetin, rhamnetin, apigenin, luteolin, naringin, hesperidin, naringenin, hesperitin, morin, phloridzin, diosmin, fisetin, vitexin, neohesperidin dihydrochalcone, flavone, glycosylrutin and genistein.

The flavonoids which are particularly preferred according to the invention are chrysin, naringin, hesperidin, naringenin, hesperetin, morin, phloridzin, diosmin, neohesperidin dihydrochalcone, flavone and, in particular, alpha-glucosylrutin of the formula

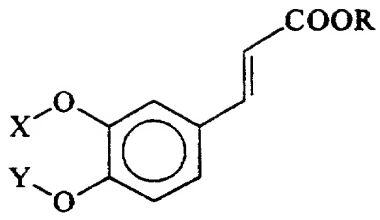


It can furthermore be advantageous in the context of the invention to use commercially available flavonoid-containing plant extracts. These can be aqueous-alcoholic or aqueous-glycolic extracts and dry extracts obtained by the customary methods.

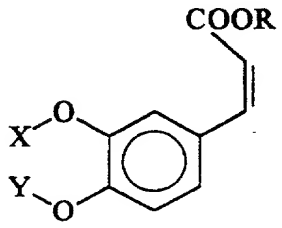
The following extracts have proved to be particularly advantageous: citrous fruit peel or kernel extract (for example Citricidal/Synthapharm), soya extract (for example Phytodermin/Chem. Laboratorium Dr. Kurt Richter GmbH), Sophora japonica extract (for example Sophorine/Solabia), Scotch thistle extract (for example Psoralen Silymarin/Mani GmbH Chemische Produkte), cat's-foot blossom extract, spinach extract and a mixed plant extract of passion flower, blackcurrant and vine leaves (AE Complex/Solabia).

Suitable cinnamic acid derivatives are, for example, hydroxycinnamic acids and derivatives thereof, it being possible for the derivatives to be, for example, those defined below.

Cinnamic acid derivatives of the general formula



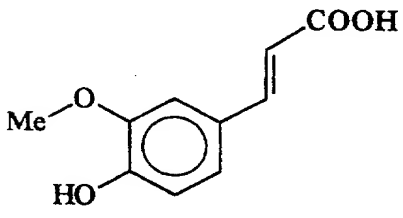
and/or active amounts of cinnamic acid derivatives of the general formula



wherein the groups X, Y and R independently of one another can be chosen from the group consisting of H and branched or unbranched alkyl having 1-18 C atoms, can be used according to the invention.

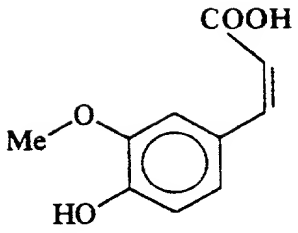
The acids or salts thereof can be used, preferably the physiologically tolerated salts, for example water-soluble salts (sodium or potassium salts).

Ferulic acid is regarded as a particularly advantageous cinnamic acid derivative in the context of the present invention. Ferulic acid (4-hydroxy-3-methoxy-cinnamic acid, caffeic acid 3-methyl ether) is characterized by the structural formula



(E-Form)

or

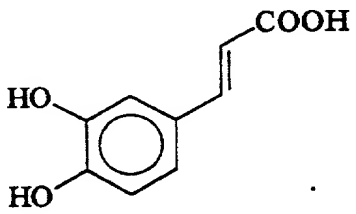


(Z-Form).

It is widespread in plants and occurs, for example, in beet crops, cereals and the latex of the umbelliferous plants Ferula asafoetida and Ferula nartex, which give it its name. The E form is a colourless crystalline solid under normal conditions, and the Z form is in the form of a yellowish oil under normal conditions.

In the context of the present invention, it is preferable to use E-ferulic acid. However, it is also advantageous, where appropriate, to employ Z-ferulic acid or any desired mixtures of E- and Z-ferulic acid.

Another derivative of cinnamic acid which is preferred according to the invention is caffeic acid, which is distinguished by the structure



It is a widespread plant acid and is contained, for example, in coffee, tobacco, poppy and dandelion.

It is also advantageous, where appropriate, to use plant extracts with a content of cinnamic acid derivatives according to the invention, in particular ferulic acid and/or caffeic acid.

The term "derivatives of caffeic acid or ferulic acid" is to be understood as meaning their cosmetically or pharmacologically acceptable esters, salts and base adducts, in particular those such as are described above for the cinnamic acid derivatives.

Preferred combinations according to the invention are combinations of one or more substances from the group consisting of the abovementioned flavonoids or combinations of one or more representatives of the flavonoids with a derivative of cinnamic acid, or also the combination with several cinnamic acid derivatives.

Combinations of flavonoids, flavone glucosides or flavonoid-containing plant extracts with ferulic acid and the combination of synthetically modified, in particular glycosylated flavonoids, such as alpha-glycosylrutin, with cinnamic acid derivatives are particularly preferred according to the invention.

The weight ratio of the cinnamic acid derivatives to the flavonoid or flavonoids is advantageously 25:1 to 1:25, preferably 5:1 to 1:5, particularly preferably about 2:1 to 1:2.

Formulations with combinations b) which comprise alpha-glucosylrutin and/or ferulic acid are particularly preferred.

The compounds of group A or those of the combination of active compounds A) and B) can be present as the sole active compounds in the formulations according to the invention.

However, in addition to active compounds A) or the combination of A) and B), the formulations according to the invention can also additionally and preferably have a content of an antioxidant or several antioxidants C).

The antioxidants C) according to the invention can advantageously be chosen from the group consisting of tocopherols and derivatives thereof. The tocopherols, also called vitamin E, are derived from the parent substance tocol (2-methyl-2-(4,8,12-trimethyltridecyl)-chroman-6-ol). The configuration 2R,4'R,8'R is attributed to α-tocopherol, which occurs naturally the most frequently and is the most important. It is occasionally also called RRR-α-tocopherol.

The tocopherol derivatives which are preferred according to the invention are α-tocopherol and its

esters, in particular α-tocopheryl acetate. Esters of acids having 2-18, in particular 2-8 C atoms are preferred.

If vitamin E and/or derivatives thereof are the antioxidant or antioxidants, it is advantageous to choose the particular concentrations thereof from the range from 0.001 to 10% by weight, based on the total weight of the formulation.

It is furthermore advantageous to use antioxidants C) from the group consisting of amino acids (for example glycine, histidine, tyrosine and tryptophan) and derivatives thereof, imidazoles (for example urocanic acid) and derivatives thereof, peptides, such as D,L-carnosine, D-carnosine, L-carnosine and derivatives thereof (for example anserine), carotenoids, carotenes (for example α-carotene, β-carotene and lycopene) and derivatives thereof, chlorogenic acid and derivatives thereof, liponic acid and derivatives thereof (for example dihydroliponic acid), aurothioglucose, propylthiouracil, thioredoxin and glutathione, and furthermore (metal)chelators (for example α-hydroxy-fatty acids, palmitic acid, phytic acid and lactoferrin), α-hydroxyacids (for example citric acid, lactic acid and malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and derivatives thereof, unsaturated fatty acids and derivatives thereof (for example γ-linolenic acid, linoleic acid and oleic acid), folic acid and derivatives thereof, ubiquinone and ubiquinol and derivatives thereof, vitamin C and derivatives (for example ascorbyl palmitate, Mg ascorbyl phosphate and ascorbyl acetate), vitamin A and derivatives (vitamin A palmitate) and coniferyl benzoate of benzoin resin, butylhydroxytoluene, butylhydroxyanisole, nordihydroguaiac resin acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and derivatives thereof, mannose and derivatives thereof, mannose and derivatives thereof, sesame oil, sesamolin, zinc and derivatives thereof (for example ZnO and $ZnSO_4$), selenium and derivatives thereof (for example selenium methionine), stilbenes and deriva-

tives thereof (for example stilbene oxide and trans-stilbene oxide) and the derivatives of these active compounds mentioned which are suitable according to the invention (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides and lipids).

The amount of the abovementioned antioxidants C) (one or more compounds) in the formulations is preferably 0.001 to 30% by weight, particularly preferably 0.05-20% by weight, in particular 1-10 % by weight, based on the total weight of the formulation.

The cosmetic and/or dermatological formulations according to the invention can have the customary composition and can be used for prophylaxis and/or for treatment of the skin in the context of a dermatological treatment or prophylaxis and/or treatment in the context of cosmetics. However, they can also be used in make-up products of decorative cosmetics.

The cosmetic and dermatological formulations according to the invention preferably comprise 0.001% by weight to 30% by weight, preferably 0.01% by weight to 10% by weight, but in particular 0.1% by weight to 6% by weight, based on the total weight, of one or more substances A) according to the invention or of the combination of A) and B).

It is advantageous according to the invention to use combinations of several antioxidants, in particular if at least one of the components is chosen from the group consisting of flavonoids and glucosides thereof and cinnamic acid derivatives.

It is particularly advantageous to use combinations of at least one compound from the flavonoids A) or derivatives thereof, at least one compound from the cinnamic acid derivatives B) and vitamin E or its derivatives C).

It is particularly advantageous to use combinations of synthetically modified, for example glycosylated flavonoids or derivatives thereof, ferulic acid and vitamin E or its derivatives. It is also particularly advantageous to use combinations of naturally occurring

flavonoids or derivatives thereof, cinnamic acid and derivatives thereof and vitamin E or its derivatives.

The weight content of active compounds from the group consisting of flavonoids and derivatives thereof and the group consisting of cinnamic acid and its derivatives can be varied in a wide range of ratios in the combinations. The weight ratio of the active compounds is preferably 20:1 to 1:20, in particular 10:1 to 1:10, particularly preferably 2:1 to 1:2.

The weight content of active compounds from the group consisting of flavonoids and derivatives thereof and the group consisting of tocopherol and its derivatives can likewise be varied within a wide range of ratios in the combinations. The weight ratio of the active compounds is preferably 20:1 to 1:20, in particular 10:1 to 1:10, particularly preferably 2:1 to 1:2.

If combinations of active compounds of the group consisting of flavonoids and derivatives thereof and the group consisting of cinnamic acid and its derivatives with the group consisting of tocopherol and its derivatives are used, the weight ratios can preferably be varied within the following limits: 20:1 to 1:20, in particular 10:1 to 1:10, particularly preferably 2:1 to 1:2.

For cosmetic or dermatological treatment and/or prophylaxis of the immunosuppression induced by UVB radiation, for protection of the immunocompetent cells, such as Langerhans cells, and for protection of cell constituents, the formulations according to the invention, preferably combinations of flavonoids and derivatives thereof, cinnamic acid and derivatives thereof and vitamin E and derivatives thereof, are applied to the skin in a sufficient amount in the manner customary for cosmetics or dermatological agents.

Cosmetic formulations according to the invention for protection of the skin can be in various forms, such as are usually employed, for example, for this type of formulation. They can thus be, for example, a solution, an emulsion of the water-in-oil (W/O) type or of the oil-

in-water (O/W) type, or a multiple emulsion, for example of the water-in-oil-in-water (W/O/W) type, a gel, a hydrodispersion, an anhydrous ointment, a solid stick or also an aerosol.

The cosmetic formulations according to the invention can comprise cosmetic auxiliaries such as are usually used in such formulations, for example UV/A and UV/B filters, preservatives, bactericides, perfumes, agents for preventing foaming, dyestuffs, pigments which have a colouring action, thickeners, surface-active substances, emulsifiers, softening substances, humidifying and/or humectant substances, fats, oils, waxes or other customary constituents of a cosmetic formulation, such as alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivatives.

If the cosmetic or dermatological formulation is a solution or lotion, solvents which can be used are:

- water or aqueous solutions;
- oils, such as triglycerides of capric or of caprylic acid, or liquid triglycerides of natural origin
- fats, waxes and other natural and synthetic fatty substances, preferably esters of fatty acids with alcohols of low C number, for example with isopropanol, propylene glycol or glycerol, or esters of fatty alcohols with alkanoic acids of low C number or with fatty acids
- silicone oils, such as dimethylpolysiloxanes, diethylpolysiloxanes, diphenylpolysiloxanes and mixed forms thereof
- alcohols, diols or polyols of low C number and ethers thereof, preferably ethanol, isopropanol, propylene glycol, glycerol, ethylene glycol, ethylene glycol monoethyl or monobutyl ether, propylene glycol monomethyl, monoethyl or monobutyl ether, diethylene glycol monomethyl or monoethyl ether and analogous products.

Mixtures of the abovementioned solvents are used in particular. In the case of alcoholic solvents, water can be a further constituent.

Emulsions according to the invention, for example in the form of a sunscreen cream, a sunscreen lotion or a sunscreen milk, are advantageous and comprise, for example, the fats, oils, waxes and other fatty substances mentioned, as well as water and an emulsifier such as is usually used for such a type of formulation.

Gels according to the invention usually comprise alcohols of low C number, for example ethanol, isopropanol, 1,2-propanediol, glycerol and water, or an above-mentioned oil, in the presence of a thickener, which is preferably silicon dioxide or an aluminium silicate in the case of oily-alcohol gels and is preferably a polyacrylate in the case of aqueous-alcoholic or alcoholic gels.

Anhydrous cosmetic and dermatological formulations, such as ointments or skin oils, according to the invention are advantageous and comprise, for example, the fats, oils, silicone oils, waxes and other fatty substances mentioned.

Solid sticks according to the invention comprise, for example, naturally occurring or synthetic waxes, fatty alcohols or fatty acid esters. Lip care sticks are preferred.

Suitable propellants for cosmetic or dermatological formulations according to the invention which can be sprayed from aerosol containers are the customary known readily volatile, liquefied propellants, for example hydrocarbons (propane, butane and isobutane), which can be employed by themselves or as a mixture with one another. Compressed air can also advantageously be used. The expert of course knows that there are propellant gases which are non-toxic per se and which would be suitable in principle for the present invention, but which should nevertheless be omitted because of an unacceptable action on the environment or other concomitant circumstances, in particular fluorohydrocarbons and fluorochlorohydrocarbons (CFCs).

The formulations according to the invention can furthermore preferably comprise substances which absorb

UV radiation in the UVB range, the total amount of the filter substances being, for example, 0.1% by weight to 30% by weight, preferably 0.5 to 10% by weight, in particular 1 to 6% by weight, based on the total weight of the formulation, in order to provide cosmetic formulations which protect the skin from the entire range of ultraviolet radiation. They can also be used as sunscreen agents.

The UVB filters can be oil-soluble or water-soluble. Oil-soluble substances which may be mentioned are, for example:

- 3-benzylidenecamphor derivatives, preferably 3-(4-methylbenzylidene)camphor and 3-benzylidenecamphor;
- 4-aminobenzoic acid derivatives, preferably 2-ethylhexyl 4-(dimethylamino)benzoate and amyl 4-(dimethylamino)benzoate;
- esters of cinnamic acid, preferably 2-ethylhexyl 4-methoxycinnamate and isopentyl 4-methoxycinnamate;
- esters of salicylic acid, preferably 2-ethylhexyl salicylate, 4-isopropylbenzyl salicylate and homomenthyl salicylate;
- derivatives of benzophenone, preferably 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxy-4'-methylbenzophenone and 2,2'-dihydroxy-4-methoxybenzophenone;
- esters of benzalmalonic acid, preferably di(2-ethylhexyl) 4-methoxybenzalmalonate; and
- 2,4,6-trianilino-(p-carbo-2'-ethyl-1'-hexyloxy)-1,3,5-triazine.

Water-soluble substances which may be mentioned are, for example:

- salts of 2-phenylbenzimidazole-5-sulphonic acid, such as its sodium, potassium or its triethanolammonium salt, and the sulphonic acid itself;
- sulphonic acid derivatives of benzophenones, preferably 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid and its salts; and
- sulphonic acid derivatives of 3-benzylidenecamphor, such as, for example, 4-(2-oxo-3-bornylidenemethyl)-benzenesulphonic acid, 2-methyl-5-(2-oxo-3-bornylidene-

methyl)-benzenesulphonic acid and its salts.

The list of UVB filters mentioned, which can be used in combination with the active compounds according to the invention, is not of course intended to be limiting.

The invention also relates to the combination of one or more active compounds according to the invention with one or more UVB filters, and cosmetic or dermatological formulations according to the invention which also comprise one or more UVB filters.

It may also be advantageous to combine one or more active compounds according to the invention with UVA filters which have usually been contained to date in cosmetic and/or dermatological formulations. These substances are preferably derivatives of dibenzoylmethane, in particular 1-(4'-tert-butylphenyl)-3-(4'-methoxyphenyl)propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl)propane-1,3-dione. The invention also relates to these combinations and formulations which comprise these combinations. The amounts used for the UVB combination can be employed.

Advantageous formulations are furthermore obtained if the active compounds according to the invention are combined with UVA and UVB filters.

Cosmetic formulations comprising active compounds according to the invention can also comprise inorganic pigments which are usually used in cosmetics for protecting the skin from UV rays. These are oxides of titanium, zinc, iron, zirconium, silicon, manganese, aluminium and cerium and mixtures thereof, as well as modifications in which the oxides are the active agents. The pigments are particularly preferably those based on titanium dioxide.

The invention also relates to these combinations of UVA filters and/or UVB filters and pigment and to formulations which comprise this combination. The amounts mentioned for the above combinations can be used.

Unless stated otherwise, all the amounts data, contents and percentage contents are based on the weight and the total amount or on the total weight of the

formulations.

The following examples are intended to illustrate the present invention, without limiting it.

Example 1

W/O cream

	% by weight
Paraffin oil	10.00
Petrolatum	4.00
Wool wax alcohol	1.00
PEG 7-hydrogenated castor oil	3.00
Aluminium stearate	0.40
Diosmin	0.50
Ferulic acid	0.50
Glycerol	2.00
Water, preservative and perfume	to 100.00

Example 2

W/O cream

	% by weight
Paraffin oil	20.00
Petrolatum	4.00
Glucose sesquiisostearate	2.00
Aluminium stearate	0.40
α-Glucosylrutin	1.00
Caffeic acid	0.50
Vitamin E acetate	1.00
Glycerol	5.00
Water, preservative and perfume	to 100.00

Example 3

O/W lotion

	% by weight
Paraffin oil	8.00
Isopropyl palmitate	3.00
Petrolatum	4.00
Cetearyl alcohol	2.00
PEG 40-castor oil	0.50
Sodium cetearyl sulphate	0.50
Sodium carbomer	0.40
Ferulic acid	0.50
Phloridzin	0.20
Glycerol	3.00
α-Tocopherol	0.20
Octyl methoxycinnamate	5.00
Butylmethoxydibenzoylmethane	1.00
Water, preservative and perfume	to 100.00

Example 4

O/W cream

	% by weight
Paraffin oil	7.00
Avocado oil	4.00
Glyceryl monostearate	2.00
Sodium stearate	1.00
Ferulic acid	0.50
Sophora japonica extract (Sophorine/Solabia)	0.80
Sodium phytate	1.00
Titanium dioxide	1.00
Sodium lactate	3.00
Glycerol	3.00
Water, preservative and perfume	to 100.00

Example 5

Lip care stick

	% by weight
Hydrogenated castor oil	4.00
Ceresin	8.00
Beeswax	4.00
Carnauba wax	2.00
Petrolatum	40.00
α-Glycosylrutin	0.10
β-Carotene	0.10
Caffeic acid	0.30
Paraffin oil, pigments and dyestuffs	to 100.00

Example 6

Lip care stick

	% by weight
Isopropyl lanolate	10.00
Acetylated lanolin	4.00
Beeswax, bleached	9.00
Carnauba wax	4.00
Petrolatum	40.00
Morin	0.10
Tocopheryl acetate	0.10
Ferulic acid	0.10
Paraffin oil, pigments and dyestuffs	to 100.00

Example 7

Liposome-containing gel

		% by weight
Lecithin		6.00
Shea butter		3.00
Ferulic acid		0.50
Neohesperidin dihydrochalcone		0.10
Tocopherol		0.20
Biotin		0.08
Sodium citrate		0.50
Glycine		0.20
Urea		0.20
Sodium PCA		0.50
Hydrolysed collagen		2.00
Xanthan gum		1.40
Sorbitol		3.00
Water, preservative and perfume	to	100.00

Example 8

Gel

		% by weight
Carbopol 934 P		2.00
Triethanolamine		3.00
Ferulic acid		0.50
Hesperitin		0.10
Tocopherol acetate		0.20
Polyoxyethylene sorbitan fatty acid ester (Tween 20)		0.50
Glycerol		2.00
Sodium PCA		0.50
Hydrolysed collagen		2.00
Water, preservative and perfume	to	100.00

Example 11

Sunscreen emulsion

	% by weight
Cyclomethicone	2.00
Cetearyl alcohol + PEG 40-hydrogenated castor oil + Sodium cetearyl sulphate	2.50
Glyceryl lanolate	1.00
Caprylic acid/capric acid triglyceride	0.10
Laurylmethicone copolyol	2.00
Octyl stearate	3.00
Castor oil	4.00
Glycerol	3.00
Acrylamide/sodium acrylate copolymer	0.30
Hydroxypropylmethylcellulose	0.30
Octyl methoxycinnamate	5.00
Butyl-methoxy-dibenzoylmethane	0.50
Sophora japonica extract (Sophorine/Solabia)	0.70
Tocopheryl acetate	1.00
Na_3HEDTA	1.50
Perfume, preservative, dyestuffs	as desired
H_2O, completely desalinated	to 100.00

Example 12

Sunscreen emulsion

	% by weight
Cyclomethicone	2.00
Cetearyl alcohol + PEG 40-hydrogenated castor oil + Sodium cetearyl sulphate	2.50
Glyceryl lanolate	1.00
Caprylic acid/capric acid triglyceride	0.10
Laurylmethicone copolyol	2.00
Octyl stearate	3.00
Castor oil	4.00
Glycerol	3.00
Acrylamide/sodium acrylate copolymer	0.30
Hydroxypropylmethylcellulose	0.30

Example 9

Sunscreen emulsion

	% by weight
Cyclomethicone	2.00
Cetyldimethicone copolyol	0.20
PEG 22-dodecyl copolymer	3.00
Paraffin oil (DAB 9)	2.00
Caprylic acid/capric acid triglyceride	5.80
Octylmethoxycinnamate	5.80
Butyl-methoxy-dibenzoylmethane	4.00
Hesperidin	0.50
Tocopheryl acetate	0.50
$ZnSO_4$	0.70
Na_4EDTA	0.30
Perfume, preservative, dyestuffs	as desired
H_2O, completely desalinated	to 100.00

Example 10

Sunscreen emulsion

	% by weight
Cyclomethicone	2.00
Cetyldimethicone copolyol	0.20
PEG 22-dodecyl copolymer	3.00
Paraffin oil (DAB 9)	2.00
Caprylic acid/capric acid triglyceride	5.80
Octyl methoxycinnamate	5.80
Butyl-methoxy-dibenzoylmethane	4.00
Naringin	0.25
Ferulic acid	0.50
Tocopherol	0.50
$ZnSO_4$	0.70
Na_4EDTA	0.30
Perfume, preservative, dyestuffs	as desired
H_2O, completely desalinated	to 100.00

Octyl methoxycinnamate	5.00
Butyl-methoxy-dibenzoylmethane	0.75
Extract of passion flower, blackcurrant and grape leaves (AE Complex/Solabia)	2.50
Ferulic acid	0.30
Na_3HEDTA	1.50
Perfume, preservative, dyestuffs	as desired
H_2O, completely desalinated	to 100.00

Example 13

Massage cream

	% by weight
Stearyl alcohol	2.00
Petrolatum	4.00
Dimethicone	2.00
Isopropyl palmitate	6.00
Cetearyl alcohol	4.00
PEG 40-hydrogenated castor oil	2.00
Tocopherol	0.50
Scotch thistle extract (Pronalen Silymarin/Mani GmbH)	0.30
Glycerol	3.00
Water, preservative and perfume	to 100.00

Example 14

Hair lotion

	% by weight
Ethanol	40.00
Diisopropyl adipate	0.10
Perfume	0.10
PEG 40-hydrogenated castor oil	0.20
Naringenin	0.10
Tocopheryl acetate	0.10
Dyestuff, preservative	as desired
Water	to 100.00

Example 15

Hair lotion

	% by weight
Isopropyl alcohol	45.00
Cat's-foot blossom extract (Helicrysum)	1.00
Propylene glycol	0.50
Perfume, dyestuff, preservative	as desired
Water	to 100

Example 16

Spray formulation

	% by weight
Naringenin	0.10
Tocopherol	0.10
Ferulic acid	0.05
Ethanol	28.20
Perfume	as desired
Propane/butane 25/75	to 100

Evidence of the action:

The advantageous properties of the present invention are to be illustrated below with the aid of an experiment.

The UVB mixed lymphocyte reaction method (UVB-MLR) was used as the model for the immunosuppressing action of UVB radiation. The UVB-MLR is a method of analyzing the effects of test substances on UVB-induced suppression of a cellular immune response. It is a modification of the MLR, an immunological in vitro standard method which serves as a measure of the activation and functionalization of the T-lymphocyte system.

For this purpose, the test substances were added to the cell cultures in various concentrations. A Phillips TL 20W/12 lamp was used as the source of irradiation.

7.5 mJ UVB/cm^2, 15 mJ UVB/cm^2 and 30 mJ UVB/cm^2 were employed as the irradiation dose.

Mononuclear cells from the peripheral blood of two healthy human donors are purifed by means of density

gradient centrifugation and cultured together in microtitre plates. The individual culture here is composed of 3.0×10^5 stimulator cells treated with mitocytin (donor A) and 2.5×10^5 responder cells (donor B) (incubation at 37°C, 7.5% of CO_2, 10% of FCS (foetal calf serum) in RPMI 1640 medium).

In a "one way" MLR, the stimulator cells are arrested physiologically by the treatment with mitocytin, so that only they act as a cellular antigen for the responder cells, proliferation of which is determined via the incorporation of ^{3}H-thymidine. The responder cells are no longer recognized as an antigen by the stimulator cells.

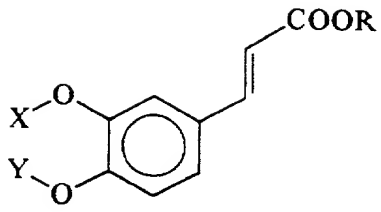
The incorporation of ^{3}H-thymidine is analyzed after separation of all the cells, that is to say stimulator and responder cells. The amount of ^{3}H-thymidine incorporated correlates with the ability to give an immune response; the less ^{3}H-thymidine incorporated, the greater the UVB immunosuppression.

In order now to determine the influence of UV light on cell proliferation (responder cells), the stimulator cells are irradiated with the corresponding UVB dose before their incubation with the responder cells. In corresponding parallel batches, the corresponding test substance is present in the culture medium during the irradiation.

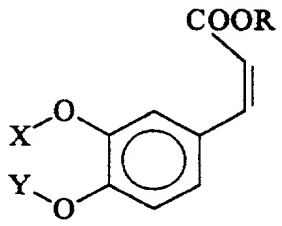
Comparisons of the proliferation of the responder cells which can be achieved in the absence and presence of test substances after co-culture with the stimulator cells allow conclusions to be drawn on immunoprotective properties of these substances at the level of UVB-induced immunosuppression.

<u>Agents according to the invention which were tested in the experiment and are active against UVB immunosuppression:</u>

Chrysin, naringen, hesperidin, naringenin, hesperitin, morin, phloridzin, diosmin, neohesperidin dihydrochalcone, flavone, glucosylrutin and cinnamic acid derivatives of the general formula



and/or active amounts of cinnamic acid derivatives of the general formula



wherein the groups X, Y and R independently of one another can be chosen from the group consisting of H and branched or unbranched alkyl having 1-18 C atoms, were used as the test substance.

Result:

A significant immunoprotective action was to be observed for all the abovementioned agents according to the invention which were tested and are active against UVB immunosuppression, and for all the three UVB dose values.

Literature on the method used:

Blain, B. et al. (1964), **Blood** 23, p. 108

Meo, T. et al. (1975), **Transplant. Proc.** 7, p. 127

Mommaas, A.M. et al. (1990), **J. Invest. Dermatol.** 95, p. 313

Marinus, C.G. et al. (1991), **J. Invest. Dermatol.** 97, p. 629

Patent Claims

1. Use of cosmetic and dermatological formulations having

a) a content of a compound or several compounds from the group consisting of flavonoids or having

b) a content of an active compound combination comprising a compound or several compounds chosen from the group consisting of flavonoids in combination with a compound or several compounds chosen from the group consisting of cinnamic acid derivatives and

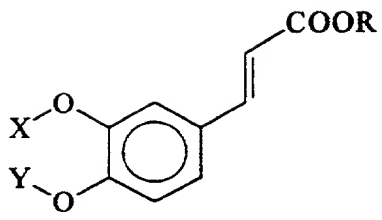
c) if appropriate an additional content of a compound or several compounds from the group consisting of antioxidants for treatment or prophylactic treatment of the immunosuppression induced by UVB radiation, in particular for treatment or prophylactic treatment of inflammatory, allergic or autoimmune-reactive symptoms, and for protecting cells which participate in the immune response of the skin.

2. Use according to Claim 1, characterized in that the flavonoids are chosen from the group consisting of alpha-glucosylrutin, alpha-glucosylmyrictrin, alpha-glucosylisoquercitrinin and alpha-glucosylquercitrin, quercitin, rutin, chrysin, kaempferol, myricetin, rhamnetin, apigenin, luteolin, naringin, hesperidin, naringenin, hesperitin, morin, phloridzin, diosmin, fisetin, vitexin, neohesperidin dihydrochalcone, flavone, glucosylrutin and genistein.

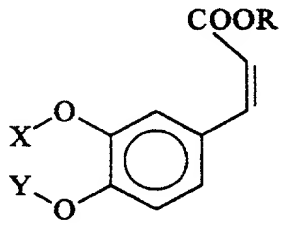
3. Use according to Claim 1, characterized in that the formulations comprise combination b).

4. Use according to Claim 1, characterized in that the formulations comprise one or more hydroxycinnamic acids.

5. Use according to Claim 1, characterized in that cinnamic acid derivatives of the formula



and/or active amounts of cinnamic acid derivatives of the general formula



wherein the groups X, Y and R independently of one another can be chosen from the group consisting of H and branched or unbranched alkyl having 1-18 C atoms, are used.

6. Formulations according to Claim 1, characterized in that they comprise caffeic acid and/or ferulic acid.

7. Use according to Claim 1, characterized in that formulations with combinations b) comprise alpha-glucosylrutin and/or ferulic acid.

Abstract

The invention relates to the use of cosmetic and dermatological formulations having
a) a content of a compound or several compounds from the group consisting of flavonoids or having
b) a content of an active compound combination comprising a compound or several compounds chosen from the group consisting of flavonoids in combination with a compound or several compounds chosen from the group consisting of cinnamic acid derivatives and
c) if appropriate an additional content of a compound or several compounds from the group consisting of antioxidants for treatment or prophylactic treatment of the immunosuppression induced by UVB radiation, in particular for treatment or prophylactic treatment of inflammatory, allergic or autoimmune-reactive symptoms, and for protecting cells which participate in the immune response of the skin.

ATTORNEY DOCKET No.: Beiersdorf 435-WCG

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled USE OF FLAVONOIDS AS IMMUNOMODULATING OR IMMUNO-PROTECTIVE AGENTS IN COSMETIC AND DERMATOLOGICAL PREPARATIONS the specification of which is attached hereto,

was filed on December 12, 1995 as

International Application No. PCT/EP95/04908 and was amended _____

and entered the U.S. National Stage on June 10, 1997 as
U.S. Application Serial No. 08/849,525.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
P 44 44 238.6 (Number)	Germany (Country)	13 December 1994 (Day/Month/Yr. Filed)	[X] yes [ ] no

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Arnold Sprung, Reg. No. 17,232; Nathaniel D. Kramer, Reg. No. 25,350; Ira J. Schaefer, Reg. No. 26,802; and Esther Steinhauer, Reg. No. 40,255 all of 120 White Plains Road, Tarrytown, New York 10591; Kurt G. Briscoe, Reg. No. 33,141; William C. Gerstenzang, Reg. No. 27,552; Paul J. Juettner, Reg. No. 20,974; and Carmella A. O'Gorman, Reg. No. 33,749 all of 660 White Plains Road, Tarrytown, New York 10591, my attorneys with full power of substitution and revocation.

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